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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,959	04/27/1999	MAURIZIO ZANETTI	P-ZA-3519	5037

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/300,959	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 6/22/05 has been entered. Claims 38-68 are currently pending and under examination at this time. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

As noted in previous office actions, claims 38, 41-42, and 44 are entitled to benefit of priority to the filing date of the parent application, April 27, 1998. Claims 39-40, 43, and 45-68 are only entitled to the benefit of priority to the filing date of the instant application, April 27, 1999.

Claim Rejections - 35 USC § 112

The rejection of claims 38, 41, and 42 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn over claim 38 and **maintained over claims 41-42**. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The rejection of claim 38 has been withdrawn in view of applicant's submission of Rizzi et al., manuscript in press, as Exhibit A, which demonstrates that delivery of plasmid vector

encoding antigen under control of a B cell specific promoter directly to the fetal liver, which has less than 5% B cells, is effective in generating immune responses against the expressed antigen.

The rejection of claims 41-42 is maintained. The evidence in Rizzi et al. does not overcome the lack of enablement for reasons of record. Unlike claim 38, claims 41-42 are not limited to the delivery of the plasmid vector to lymphoid tissue *in vivo*. The claims continue to read broadly on administering the plasmid vector *in vivo* using any site of administration. Rizzi et al. provides evidence for direct delivery of the plasmid vector to the fetal liver, a lymphoid tissue. Nothing in Rizzi et al. teaches or suggests that the delivery of the vector to non-lymphoid tissue would result in immunization. Further, neither Maloy et al., previously submitted and discussed in the previous office action, nor Castiglioni et al., newly submitted, teach or suggest delivery to non-lymphoid tissue. It is also noted, as discussed in the previous office action for Maloy et al, that both references use intra-nodal injection to target dendritic cells and do not teach or provide enabling evidence for immunization by transfecting B cells.

Finally, the applicant reiterates their argument that unpredictability is not an issue with respect to the claims and that since the claims recite that the heterologous epitopes are expressed in B cells, any unpredictability for *in vivo* targeting, referencing the evidence cited by the office - Deonarian et al. and Miller et al.- is not applicable. In response, this argument was fully considered and not found persuasive in the previous office action. As stated, case law teaches (Ex parte Forman, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or

absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or underpredictability of the art and the breadth of the claims." See also MPEP 2164.01(a). Thus, it is clear that unpredictability in the prior art is relevant to whether the claims are enabled by the instant specification. The previous office actions have stated that the specification fails to provide an enabling disclosure for specifically transfecting B cells using any route of administration. The articles cited in the previous office actions, particularly Deonarian and Miller, clearly teach that specific targeting of a nucleic acid to a particular cell was unpredictable at the time of filing. For example, Deonarain teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al., page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al., page 198, paragraph 2). These references thus establish that at the time of filing, the skilled artisan considered specifically targeting a certain cell population *in vivo* using currently available vector systems unpredictable. The previous office actions further noted that the specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to B cells *in vivo*. The specification as a whole discusses introducing the plasmid into lymphoid tissue and the working examples exemplify intrasplenic injection. The specification does not provide specific guidance or working examples

for the targeted expression of a heterologous epitope in B cells by administering plasmid DNA by intramuscular, intradermal, intratracheal, or intracerebral injection, or for the number of B cells which must be transfected and express the heterologous epitope in order to stimulate an immune response. As noted previously, the spleen contains a large number of B cells, whereas other non-lymphoid tissues, such as muscle, skin, or brain do not contain any B cells. Therefore, in view of the art recognized unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for plasmid vectors suitable for specifically targeting B cells, the lack of working examples concerning methods of targeted delivery other than intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The rejection of claim 39 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention, is withdrawn in view of applicant's amendments to the claim.

Claim Rejections - 35 USC § 103

The rejection of claims 39-40, and 43-68 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,891,432 (1999), hereafter referred to as Hoo, in view of Banerji et al. (1983) Cell, Vol. 33, 729-740, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant reiterates their arguments that there would have been no motivation to combine the teachings of Hoo et al. with those of Banerji et al. Specifically, the applicant argues that Hoo et al. and Banerji et al. do not teach "B" cells, but rather plasmacytoma or myeloma cells and that neither cell type is a B cell. In support of this argument, the applicant points to the definition of myeloma and plasmacytoma in Stedman's Medical Dictionary which says that myelomas and plasmacytomas are derived from plasma cells. According to the applicant, plasma cells are not B cells, citing Kuby, pages 212 and 216. These pages demonstrate that following B cell activation, B cells differentiate into either memory cells or plasma cells. However, it is not agreed that Kuby teaches that plasma cells are not B cells. Kuby in fact teaches in Chapter 2 that B cells include memory cells and plasma cells, see chapter 2 excerpts from Kuby, Immunology, W.H. Freeman and Company, New York reprinted from the W.H. Freeman website. Further, the pages from Kuby provided by the applicants teaches that plasma cells secrete immunoglobulin rather than present it on the cell surface in membrane form. While the specification does not specifically define "B cells" or "B lymphocytes", the specification does state that upon activation with antigen, B cells produce between 1X10-3 -8X10-3 molecules of immunoglobulin/cell/sec (see specification, page 45, lines 5-14). As taught by Kuby, the secretion of large amounts of immunoglobulin is exclusive to plasma cells. Thus, it would appear that the specification's concept of B cells, similar to the that of Kuby, does include plasma cells. As such, applicant's argument that plasma cells are not B cells is not persuasive.

The applicant is also reminded that claims 44-68 are composition claims drawn to plasmid vectors. The issue of whether plasmacytomas are "B cells" is irrelevant to these claims since the limitations of the claims are simply drawn to plasmid vectors comprising a B cell

expression element operatively linked to a nucleic acid encoding a heterologous polypeptide antigen or polypeptide antigen/cytokine fusion protein. The heavy chain Ig enhancer is only active in cells which express immunoglobulin, which clearly includes B cells. The rejection of record states that while Hoo et al. generally teaches that the genes encoding the fusion proteins are operatively linked to promoters, and gives the SV40 promoter as an example, Banerji et al. supplements Hoo by teaching a plasmid encoding the b-globin gene operatively linked to the immunoglobulin enhancer, a B cell specific expression element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific expression elements by teaching that use of the immunoglobulin heavy chain enhancer to express a heterologous gene, b-globin, results in two fold increase in the magnitude of b-globin expression compared to vectors which utilize the viral SV40 enhancer (Banerji et al., page 729, abstract, and page 731, column 2, paragraph 3). Based on the increased magnitude of gene expression using the immunoglobulin promoter versus a viral promoter such as SV40 as taught by Banerji et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the viral elements in the plasmid vectors taught by Hoo in order to increase antigen.

Therefore, for the reasons discussed above and of record, the instant rejection stands.

Allowable Subject Matter

Claim 38 is considered free of the prior art of record and allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER